

ADDISON'S DISEASE: A CASE OF TUBERCULOSIS OF THE ADRENALS.

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THE purpose of this paper is to report a case of Addison's disease, including the case history and autopsy findings. The writer is indebted to Dr. J. W. Bruner and Dr. A. C. Morgan for permission to report the case and the use of the clinical report.

During previous experience in postmortem work several cases of Addison's disease have been encountered, two of which stand out prominently. One had been considered a clinical case of Addison's disease and had been used for teaching purposes. At autopsy no lesions whatsoever of the adrenal could be demonstrated. The second case had not been diagnosed and presumably had not shown the clinical features, while at autopsy large tuberculous adrenals were found.

The present case was diagnosed clinically, presenting the classical symptoms, while at autopsy definite tuberculosis of the adrenals was demonstrated. The following clinical history obtained by Dr. Morgan presents the typical signs and symptoms of this disease:

Mr. G. S., aged forty-three years, principal of a high school.

Chief Complaint. October 30, 1920, the patient complained of a very tired feeling which has increased during the past six weeks.

Past Medical History. In November, 1918, he was sick for one week succeeding the influenza epidemic. He has had numerous attacks of tonsillitis until the removal of the tonsils four years ago. Had the usual diseases of childhood. The patient has had an active life working on a farm until twenty-five years old, when he attended the Bloomsburg Normal School and has been teaching ever since. During the summer of 1918, in Maryland, he had an attack of illness of a week in which he complained of being very tired and dizzy, but no pain. He had never had chills, but has been subject to bleeding gums for some time.

Social History. Married for the past eighteen years, but has no children. Wife never pregnant. His heaviest weight was 175 pounds twenty years ago. Average weight, 154 to 164 pounds, and about a month ago this dropped to 151½ pounds. His appetite has been good until the past week. He has been subject to bilious attacks for several years. This has been accompanied by nausea and occasional vomiting lasting for two days. This has occurred

as often as once a week, but lately about every six months. These attacks were relieved by laxatives.

History of Present Illness. The school term of 1919-20 seemed to leave the patient a little more tired than usual. He spent the summer months at Danville, Pa., caring for his father, who died at the age of seventy-seven years. At this time the patient lost considerable sleep and was under great strain. The patient returned to his school duties, and about September 15 noticed that he became extremely tired upon the least exertion. Work seemed to pile up, his strength lessened and he fell back considerably. The patient did not worry over this and had a clerk to aid him. During the past week the weakness seemed to have progressed considerably. The illness is not associated with pain, and walking short distances is accomplished without effort. Standing still causes dizziness and faintness and the patient must sit down to get relief.

Physical Examination. Face and neck are very dark, edging off at the clavicles. At times they are ashen gray. The lips are dusky and pigmented, but not the appearance of cyanosis. The gums are very much pigmented and resemble those of a bull dog. Both nipples show marked deep brown pigmentation, with well-marked lines of demarcation. No pigmentation over the axillæ or pubes. The hands show a tendency to pigmentation, but not to the same extent as does the face. From the wrist to above the elbow the discoloration is apparently due to ordinary exposure effects. The heart outline seems smaller than normal on percussion. No adventitious sounds. The lower border of the stomach is on a level with the umbilicus. The liver is five inches in depth in the right nipple line. The spleen seems increased on percussion in the left axillary line. On deep palpation under the left costal margin there is decided tenderness and apparent resistance down to the level of the umbilicus, but no distinct mass is felt. Bimanual palpation of both flanks gives some tenderness, but without definite localization. The feel of the muscles is very flabby.

Urine Analysis. (a) Amber; clear; acid; 1016; negative for albumin, sugar and indican; long, narrow hyaline casts; occasional leukocytes, epithelium and urates.

(b) 1020; acid; very faint trace of albumin; indican plus; no acetone, diacetic acid or sugar; urea, 10.56 grams per 960 cc; epithelial cells; hyaline casts (1); bacteria; amorphous urates.

(c) 1010; very faint trace of albumin; 1 hyaline and 1 granular cast; epithelial cells and bacteria.

Blood Examination. Red blood cells, 3,840,000; white blood cells, 10,200; hemoglobin, 90, Cl, 1; polynuclears, 45; large lymphocytes, 30; small lymphocytes, 32; eosinophils, 3; microcytes; macrocytes; poikilocytosis. Cells have tremendous ameboid motion. Cannot find malarial parasites in stained specimen.

Blood-pressure. Systolic, 84; diastolic, 58; pulse-pressure, 94; regular tones very soft and without murmur.

Renal Function. December 7, 1920. Reaction time, fifteen and one half minutes. Percentage in first specimen, 15; second, 10; total, 25. CO₂ in alveolar air, 40 per cent.

Blood Examination. December 3. Red blood cells, 3,690,000; white blood cells, 7,200; hemoglobin, 85 per cent; polynuclears, 72; small lymphocytes, 24; large lymphocytes, 2; neutrophils, 2.

Examination of the Chest, Roentgen Ray. Peribronchial markings are well-defined throughout both lungs. The right upper lobe extending from the apex to the first interspace anteriorly shows a definite tuberculous infiltration. The left apex shows a similar condition with several dense small calcified tubercles. The appearance of the condition of the right apex would suggest a more recent activity. Examination of the sinuses show the frontal sinuses quite large, but no evidence of any infection.

Examination of the Teeth. Subject to bleeding gums for some years. Examination shows no evidence of infection of the upper jaw. The lower right anterior bicuspid, which has been crowned, shows a pericementitis with apical infection.

The autopsy was made at the patient's residence through the courtesy of Dr. J. W. Bruner, and the following is the report:

Date of death, January 14, 1921.

Date of autopsy, January 14, 1921, 8 P.M.

Clinical Diagnosis. Addison's disease.

Cause of Death. Bilateral tuberculosis of the adrenals.

Associated Diagnosis. Acute pulmonary hypostatic congestion, bilateral. Cardiac dilatation. Chronic degenerative nephritis with pyramidal anemia. Arrested pulmonary apical tuberculosis.

Gross Description. The body was that of an adult white male, forty-three years of age, moderately well nourished, slight *livor mortis* in the dependent positions and rigor moderately marked eight hours after death. The face and exposed parts of the neck, the hands and lower arms had a dark bronzed color, due apparently to a pigmentation which had diffused and evenly distributed in the cutaneous layer. It was observed that this bronzed color was very much less marked after than before death. The pigmentation did not involve the covered portion of the body, although in these there was a pasty pallor.

The usual primary incision was made from the episternal notch to the symphysis pubis, and the breast plate was removed.

Chest. There was no fluid on either side; the lungs were partially collapsed. At both apices old pleural fibrous adhesions attached the lung to the parietal wall firmly enough on the right side to tear the lung structure during removal.

The right lung, in the uppermost portions, was pallid, soft and crepitant, with moderate lines of anthracotic markings. The dependent position, especially of the lower lobe, was darker blue in color, boggy to palpation and a considerable amount of frothy

blood-tinged fluid exuded from the cut surface. There was no evidence of consolidation. The apex of the upper lobe was torn in removal, considerably reacted by scar tissue, contained several well-circumscribed and densely fibrotic nodules which presented upon section caseous centers.

The left lung was a counterpart of the right, with the exception that the nodular involvement at the apex, while present, was less marked. This was an old process and there was no evidence of a recent flare-up.

The pericardium contained the usual amount of serous fluid, and there were no adhesions.

The heart, *in situ*, was dilated and the large vessels on the venous side were dilated and filled with blood. This dilatation involved the right auricle. The coronary vessels were partially dilated with no evidence of fibrosis.

The thymus gland showed distinctly its outline and was removed without much difficulty. Upon section the structure was somewhat dense by reason of a fibrosis, but the replacement by fat predominated. At the upper positions of the thymus and upon both sides of the vessels several large masses of darkly pigmented lymph nodes were found. There was no other involvement of lymph nodes in the neck.

The thyroid was not enlarged and its gross appearance was that of the normal pink, fleshy color and character.

Abdomen. The abdomen was flat. The omentum was thick and well nourished. This tendency to the deposition of fat was also noticed in the subcutaneous areas here at the expense of muscular development.

The usual anatomy of the abdominal cavity was preserved; the appendix was normal and the gall-bladder slightly distended, but free from adhesions. The lower border of the liver had the usual outline, being at the costal margin. The liver was a dark, slaty color with a tendency to swelling of the parenchyma. The bile ducts were patulous and free from stones.

The spleen was slightly enlarged, of a slaty gray color, and upon section the splenic pulp was dark blue with the follicles standing out distinctly.

Suprarenals. Both organs were involved in exactly the same manner and the process was sharply confined to the suprarenal bodies. There had been no extension from within outward and no evidence of surrounding involvement. *In situ* the organs occupied their usual positions, bound in a considerable amount of perirenal fat. Upon palpation they could easily be distinguished by their peculiar outline. If anything, they felt somewhat firmer than usual. There was no enlargement. Upon excision, attempting to dissect out the bodies from their surrounding fat, the usual brownish or yellowish character of the glands was found to have entirely

disappeared. Its place was taken in part by a fibrosis of the capsule and in part by an irregular trabecular type of firm, whitish tissue enclosing areas of softening more like a coagulation necrosis than an actual suppuration or caseation. The color of these softened areas corresponded to the color of the surrounding fat. If one had not been sure of the palpation of these organs and their position after excision and incision, nothing could be recognized which would fix their character. In other words the process present had involved the entire glandular structure, both cortex and medulla. The remaining substance was a mass of fat enclosing the capsule and trabeculae of fibrous tissue enmeshing areas of necrosis. This was a most unusual finding, the picture quite definite in itself and after a minute search no evidence of other similar involvement, with the exception of the healed caseous nodules in both apices, which were like all other similar lesions, could be found.

The kidneys were small, dark blue in color, bound down in considerable fat, capsules slightly adherent, cut edges bulged distinctly, cortex granular, with paler mottled lines. The pyramids stood out as almost pallid white islands in the midst of the kidney substance. There was no involvement of the ureters or bladder.

Upon dissecting out the retroaortic vessels several masses of glandular tissue were encountered. Some of these were distinctly hemolymph node types while others presented the fleshy character of lymphoid hyperplasia.

The pancreas had the usual salmon-pink color and upon section a normal meaty character. There was no fatty replacement and no fibrosis.

Microscopical Examination. *Kidney.* The section presents the pyramidal positions with increased hyalinized periglandular connective tissue. The cortex presents dilation and stasis of red blood cells in all capillaries, especially the tubular ones. In the endothelial cells of these capillaries and in the epithelial cells of the tubular epithelium there is a deposition of refractive granules of pigment. The tubular cells are swollen and granular, with distinct nuclei. The glomerules have slightly fibrotic capsules, desquamation of epithelial cells and some reduction in the size of the tufts.

Diagnosis: Chronic degenerative nephritis with passive congestion and metabolic pigmentation.

Liver. The section presents a diffuse appearance. The lobular structure is lost by reason of diminution of perilobular tissue. This is especially true of biliary capillaries and bile ducts. Decided atrophy of these elements is present. The central lobular veins are not distended but the interlobular capillaries are the seat of a diffuse but moderate stasis. Their endothelial lining cells are filled with granular pigment. The liver cells are not sharply defined but run into one another, with some obscurity of nuclei, and positions corresponding to the central lobular veins show vacuolization of fatty metamorphosis.

Diagnosis: Chronic degenerative hepatitis with diffuse passive congestion, fatty metamorphosis, metabolic pigmentation and atrophy of biliary system.

Spleen. The section presents a diffuse appearance and does not show the prominence of follicles noted grossly. The trabeculae are not thickened, but in places are prominent. There is a marked deposition of pigment of the same character as elsewhere, but in greater bulk. The lymphoid cells are closely packed and here and there endothelial cells have proliferated. Congestion is diffuse and stasis of red blood cells marked.

Diagnosis: Chronic lymphoid splenitis with passive congestion and metabolic pigmentation.

Thyroid. The section presents a compact picture of one of glandular activity. The epithelial cells are single layered, but show some proliferation as new glands. There are areas of lymphocytes and the capillaries are uniformly the seat of stasis of red blood cells. There is no pigment except in the endothelial cells of large vessel walls.

Diagnosis: Chronic interstitial thyroiditis with congestion.

Pancreas. The sections of pancreas present well-stained pancreatic cells, taking the usual predominance of basic color. The islands of Langerhans stand out clearly. All vessels, both capillaries and large, are filled with red blood cells, the same congestion as noted in other specimens. There is a diffuse deposition of pigment throughout the section not alone confined to the epithelial cells but decidedly concentrated in the midst of the cells of the islands of Langerhans.

Diagnosis: Congestion and metabolic pigmentation.

Thymus. The usual fibro-fatty tissue is present here with numerous large bloodvessels, and scattered throughout this are areas of lymphoid structure surrounding remnants of Hassall's corpuscles. The latter are small, flattened whorls of epithelial cells apparently containing congested red blood cells. In the lymph structure about these the type of cell is a small lymphocyte similar to those of the lymph node extending irregularly into the fatty connective tissue. There is no pigment present in this section.

Lymph Nodes. Numerous sections of lymph nodes taken from the peribronchial position show a large amount of pigment deposition, some of which is anthracotic, but a large amount of which is the same metabolic character as noted in the other sections. Capillaries are congested. There is a slight proliferation of lymphoid cells with irregular areas of endothelial cells, as noted in the spleen.

Retroperitoneal lymph nodes show the characteristic lymphocytic hyperplasia, congestion of the capillaries is moderate and only a small amount of pigment is present.

Sections taken from the retroaortic positions show numerous areas of lymphatic structure with markedly congested vessels. The

lymphoid proliferation is not as marked as elsewhere nor is the endothelial hyperplasia apparent.

Adrenals. There is no normal adrenal structure microscopically. There is a diffuse cellular proliferation, which cells are of several types—endothelial, plasma, endotheloid and fibroblastic. The endothelioids have grouped themselves into regular tubercle formation which in places has gone on to areas of necrotic hyaline and caseation. Here and there may be seen large giant cells. This process is not as sharply defined microscopically by the capsule of the adrenal, which in places is hyalinized, as it was apparently in the gross specimen; however, it does not penetrate to any considerable extent into the surrounding fatty connective tissue. As noted grossly the necrotic hyaline is more abundant than caseation, with a tendency to large conglomerate tubercles rather than miliary types.

Diagnosis: Caseous tuberculosis.

Guinea-pig Test. Subcutaneous emulsion of adrenal into two pigs. Both pigs died March 29, 1921. Autopsy showed identical findings. A small nodule over the site of the injection, tubercles with swelling and congestion in the spleen, liver, lungs and peribronchial lymph nodes. A small bloody exudate with some nodules on peritoneum.

Smear from Spleen: Tubercle bacilli positive.

Comment. Cases of true Addison's disease, tuberculosis of the adrenals, while they are not rare, are uncommon enough to warrant their report. In a study of this case there are several interesting features open to discussion and lines along which further work should be undertaken.

In the first place the presence of an advanced and directly confined active tuberculosis in both adrenals and the finding of a completely arrested and healed tuberculosis in the apices of the lungs is a hard one to explain. There has evidently been no fresh activity arising from the lungs. The apical infection may have preceded the adrenal infection or may have been coincident with it, or even the so-called healed lesions may have given up virulent tubercle bacilli which have secondarily lodged in the adrenals.

That this disease, at one time, must have been a bacteriemia, at least of a temporary nature, is quite evident. It would seem to the writer that the pulmonary lesions occurred at one time and were completely arrested while the adrenal lesion received its dosage through another portal of entry not apparent at the time of autopsy. The question as to whether a strain of tubercle bacilli with a predilection for the adrenal is only a supposition, and on the other hand any chemical combination which the adrenals might have had in attracting the tubercle bacilli to that particular site would, it seems to me, be a decided possibility. The complete absence of tuberculosis elsewhere in the body, in the presence of such an active lesion as found in the adrenals, offers a further field for study. That the

organisms had any predilection for the adrenal gland is more certainly ruled out by the fact that when inoculated into the guinea-pig they produced in duplicate the usual experimental tuberculosis.

The nature of the pigment, at least from its morphological character, would seem to be similar to that found in the hemozoin pigment of malaria, and indeed the distribution was very similar, being found in large quantities in the spleen and in the endothelial cells of capillaries throughout the sections.

That any of the other glands of internal secretion, as, for instance the thyroid or the retroaortic lymph nodes, were stimulated does not seem likely, although in the thyroid a distinct interstitial thyroiditis of a lymphoid nature was present.

The appearance of the capillaries in all of the sections showing a uniform stasis of red blood cells should be noted in the nature of a passive congestion with the characteristics of an active type. That the disease was due to a tubercle bacillus the case conclusively proves by animal experiment, in which the usual tuberculosis was produced and from which tubercle bacilli were cultured.

It is unfortunate that chemical studies were not carried out, either during the lifetime of the patient or upon the remnant of the adrenal gland obtained at autopsy. It would seem that the entire adrenal gland was eventually destroyed and replaced by a tuberculous process of a rather highly cellular character. That this produced a general diminution of adrenalin is quite apparent from the clinical history, but chemico-physiological studies of the gland remnant would have been interesting.

Conclusions. This report covers a case of Addison's disease presenting the characteristic clinical symptoms of progressive weakness associated with bronzing of the skin.

Pathologically the case presented a typical localized and focalized tuberculosis of both adrenals with an arrested apical pulmonary tuberculosis of a probable unassociated nature. The direct smear from the adrenal showed the presence of tubercle bacilli in large numbers. Animal inoculation with crushed material from the adrenal produced experimental tuberculosis from which tubercle bacilli were obtained in culture.